CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-777

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

FEB 29 2000

IND#: ——(SN-124)

APPLICANT: Fujisawa

NAME OF DRUG: Protopic (Tacrolimus oinment)

TYPE OF REVIEW: Animal Carcinogenicity

DOCUMENTS REVIEWED: —— Final Report on Study 3-A20

PHARM/TOX INPUT: Barabara Hill, HFD-540

I. Background

One animal carcinogenicity study in mice was included in the report provided. The purpose of this study was to assess the carcinogenic potential of tacrolimus ointment when administered by once daily dermal application to mice.

II. The Mouse Study

a. Design

In this study 350 male and 350 female B6C3F$_1$ mice were assigned to 2 control (1 untreated and 1 vehicle) and 5 dose groups (50/sex/group). Animals in the treated groups receieved tacrolimus ointment by once daily dermal application to 40% of total body surface area for 104 weeks at dose levels of 0.03%, 0.1%, 0.3%, 1%, and 3% tacrolimus. Animals were shaved on the dorsal trunk weekly before and during application. Mice were randomized into groups by weight, using a computer generated randomization algorithm.

Animals were observed and their viability judged twice daily. Animals were euthanized if their survival was judged unlikely. General health, physical appearance, behavior, and toxicities were observed every four weeks. Location and progression of skin tumors were observed weekly.

On completion of the 104 week treatment period, all surviving mice were killed. There were no interim sacrifices. After sacrifice, all animals were in groups 0-3 were subject to microscopic examination of tissues from listed in table 8 of the sponsor's report.

b. Sponsor's Analyses

The log-rank test and the Kaplan-Meier curves were used to estimate and to test homogeneity of, survival. Body weight and food consumption were compared using either ANOVA or Kruskal-Wallis. The choice of analysis was based on a preliminary Bartlett's test for homogeneity of variances. The FDA reviewer notes that this procedure is unnecessarily complicated and that the preliminary use of a test with low power to choose the final test has undocumented effects of the operating characteristics of the overall test. With a straight-forward randomization algorithm, the ANOVA has valid level regardless of homogeneity of the variances.

The Peto mortality-prevalence test to analyze tumor data.

There were statistically significant decreases in body weight, food consumption, and survival in the three highest dose groups (0.3%, 1%, and 3%). Consequently, data from these dose groups were excluded from analyses of the tumor data.

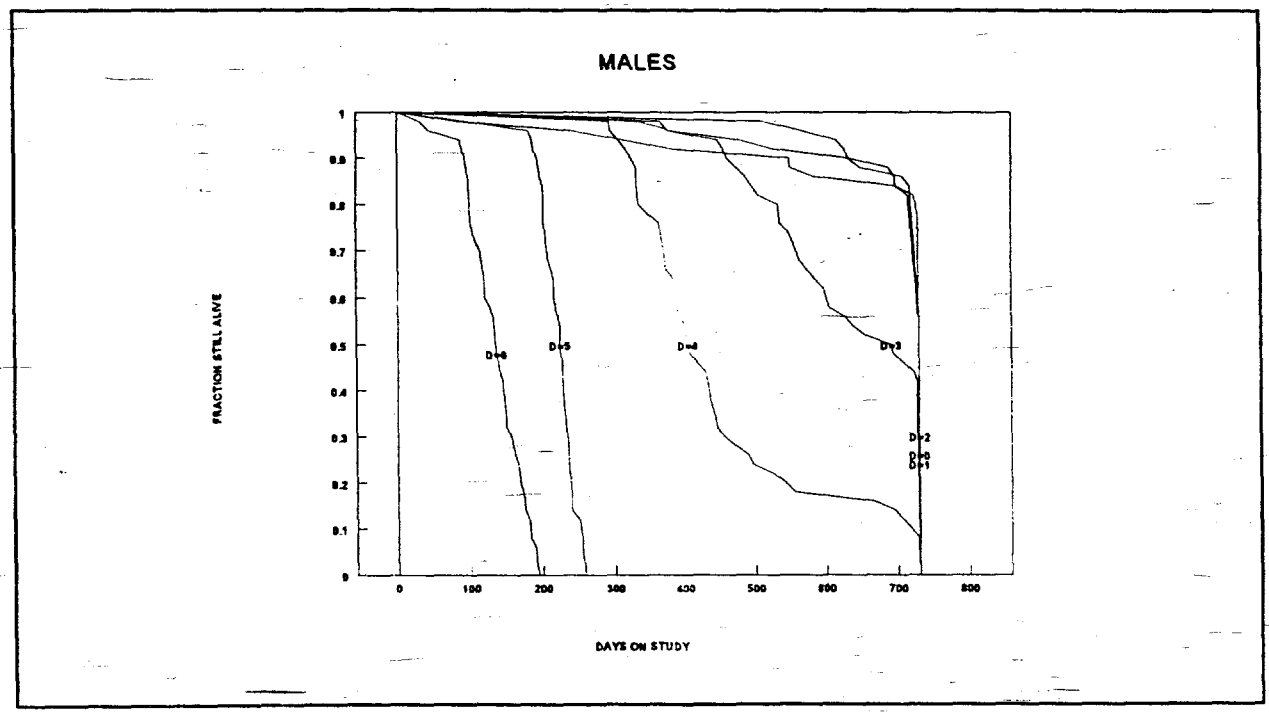
The sponsor found no statistically significant increases in tumor incidence in females. They found a statistically significant increase in hemolymphoretic tumors in males, with a p-value <0.003. The FDA reviewer notes that the claims of no statistically significant increase in hemolymphoretic tumors in females is conspicuously in error.

c. Reviewer's Analyses and Comments

The FDA reviewer independently performed analyses on the survival and tumor data. In the survival analysis, the reviewer plotted Kaplan-Meier curves for each dose group and used the log-rank test to test for differences among dose groups. For non-fatal tumors discovered at time of death, dose groups were compared using the Cochrane-Armitage trend test for tables stratified by time of death. For this analysis, time of death was divided into 4 periods, each 26 weeks long. For fatal tumors, a log rank test for time to death was used to compare dose groups. There were no discoverable tumors. Despite the fact that the drug was applied to the skin, all tumors were reported as first detected at time of death.

Survival Analysis:

The Kaplan-Meier estimates of the survival curves for the control and 6 dose groups are given in figure 1. One can see that the three highest dose groups experienced very high toxicity and that even the fourth highest dose group experienced a death reate of 50% prior to the conclusion of the study. The applicant and the FDA reviewer both treated the fourth highest dose group as the MTD and exlcuded the three highest dose groups from subsequent analyses. No tumors were reported in the two highest dose groups and tumor incidence rate in the third highest dose group was much lower than in the fourth highest group.



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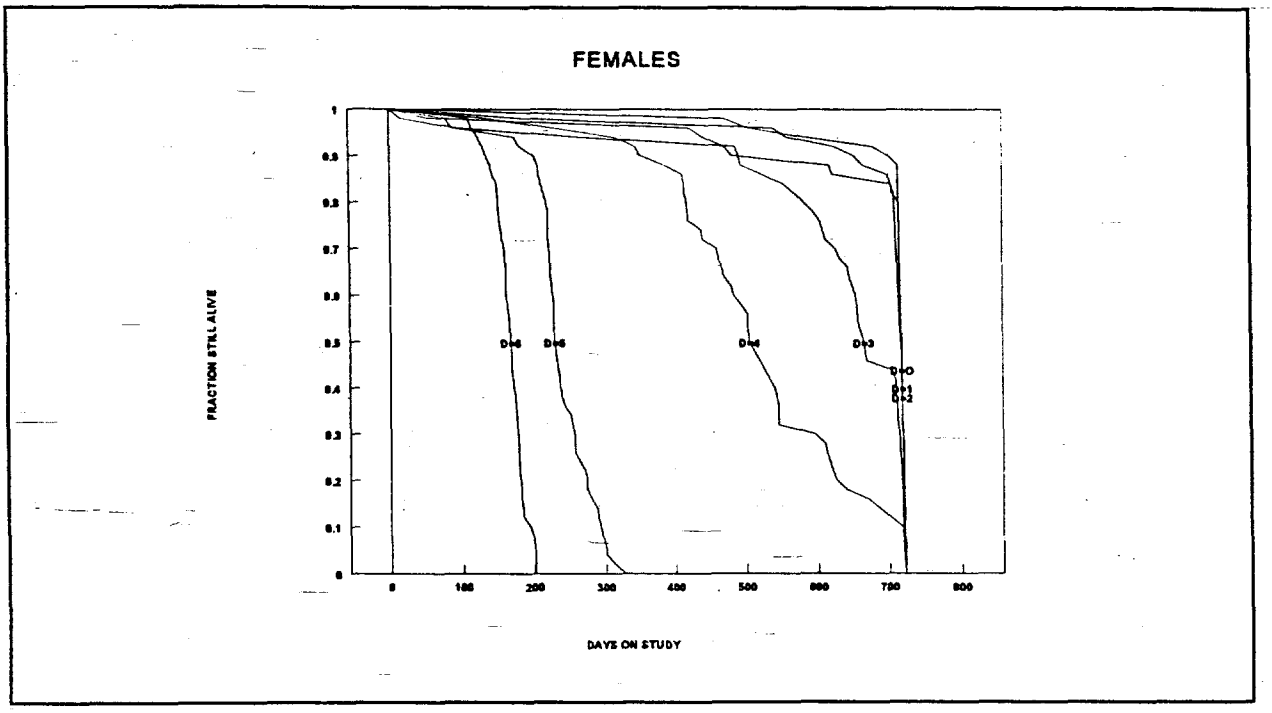

Non-Fatal Tumor Analysis:

There were no non-fatal tumors that were statistically significant by the Cochran-Armiatge trend test.

Fatal Tumor Analysis:

There was only one organ system which showed any statistically significant increase in fatal tumors. There was a highly statistically significant increase two types of tumors in the hemolymphoretic system.

Among tumors of the hemolymphoretic system, there was no significant increase in histiocytic sarcoma, lymphocytic lymphoma, or plasmacytoma in either sex. There were statistically significant increases in pleomorphic lymphoma and in undifferentiated lymphoma.

The observed incidence rates for pleomorphic and undifferentiated lymphomas are given in the four tables below. One can see that the incidence rate is clearly non-linear as a function of dose group. The statistically significant increase occurs in the highest dose group only.

Pleomorphic Lymphomas of Hemolymphoretic System/Animals at Risk in Female Mice				
Time of Death	Dose Group			
	0=untreated	1=vehicle	2=0.03%	3=0.1%
<26 wks	0/1	0/0	0/0	1/2
26-52 wks	0/0	0/0	0/1	0/1
52-78 wks	1/4	0/2	0/1	1/3
78-104 wks	11/45	6/48	14/48	26/44

Pleomorphic Lymphomas of Hemolymphoretic System/Animals at Risk in Male Mice				
Time of Death	Dose Group			
	0=untreated	1=vehicle	2=0.03%	3=0.1%
<26 wks	0/0	0/1	0/0	0/0
26-52 wks	0/1	0/1	0/0	0/0
52-78 wks	1/3	0/2	0/1	4/12
78-104 wks	6/46	2/46	4/49	21/38

Undifferentiated Lymphomas of Hemolymphoretic System/Animals at Risk in Female Mice				
Time of Death	Dose Group			
	0=untreated	1=vehicle	2=0.03%	3=0.1%
<26 wks	0/1	0/0	0/0	1/2
26-52 wks	0/0	0/0	0/1	0/1
52-78 wks	0/4	0/2	0/1	2/3
78-104 wks	3/45	1/48	3/48	11/44

Undifferentiated Lymphomas of Hemolymphoretic System/Animals at Risk in Male Mice				
Time of Death	Dose Group			
	0=untreated	1=vehicle	2=0.03%	3=0.1%
<26 wks	0/0	0/1	0/0	0/0
26-52 wks	0/1	0/1	0/0	0/0
52-78 wks	0/3	0/2	0/1	1/12
78-104 wks	0/46	1/46	2/49	3/38

The p-values for the Cochran-Armitage trend test are given in the following table.

P-values for Mouse Hemolymphoretic Tumors by Tumor Type and Sex			
Tumor Type	Sex	Cochran-Armitage P-value	
		Including Untreated	Excluding Untreated
Pleomorphic Lymphoma	Females	0.0001	<0.0001
	Males	<0.0001	<0.0001
Undifferentiated Lymphoma	Females	0.0005	0.0001
	Males	0.033	0.18

The p-values for the pairwise tests are given in the following table. One can see that the statistically significant increase in tumor incidence occurs in the 0.1% dose group.

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P-values for Mouse Hemolymphoretic Tumors by Tumor Type and Sex						
Tumor Type	Sex	Pairwise P-values				
		Compared to Untreated			Compared to Vehicle	
		Vehicle	0.03%	0.1%	0.03%	0.1%
Pleomorphic Lymphoma	Females	0.11	0.68	0.0009	0.046	<0.0001
	Males	0.10	0.37	0.0001	0.44	<0.0001
Undifferentiated Lymphoma	Females	0.28	0.94	0.004	0.31	0.0005
	Males	0.32	0.17	0.05	0.60	0.20

The Kaplan-Meier curves for the estimated times to fatal pleomorphic and undifferentiated lymphomas are given in the two following figures. One can notice that by week 104 in dose group 4 (0.1% tacrolimus) about 25% of females died from pleomorphic lymphomas and about 20% of females died from undifferentiated lymphomas. In the same dose group, about 25% of males died by week 104 from pleomorphic lymphomas and about 10% of males died from undifferentiated lymphomas. These account for approximately 50% of the deaths in males and most of the deaths in females. The p-values for the log-rank tests for a dose effect on time to tumor are given in the table below. These p-values were obtained only comparing vehicle, 0.03% dose, and 0.1% dose.

P-values for Mouse Hemolymphoretic Tumors by Tumor Type and Sex		
Tumor Type	Sex	Log Rank P-value
Pleomorphic Lymphoma	Females	0.004
	Males	<0.0001
Undifferentiated Lymphoma	Females	0.0006
	Males	0.019

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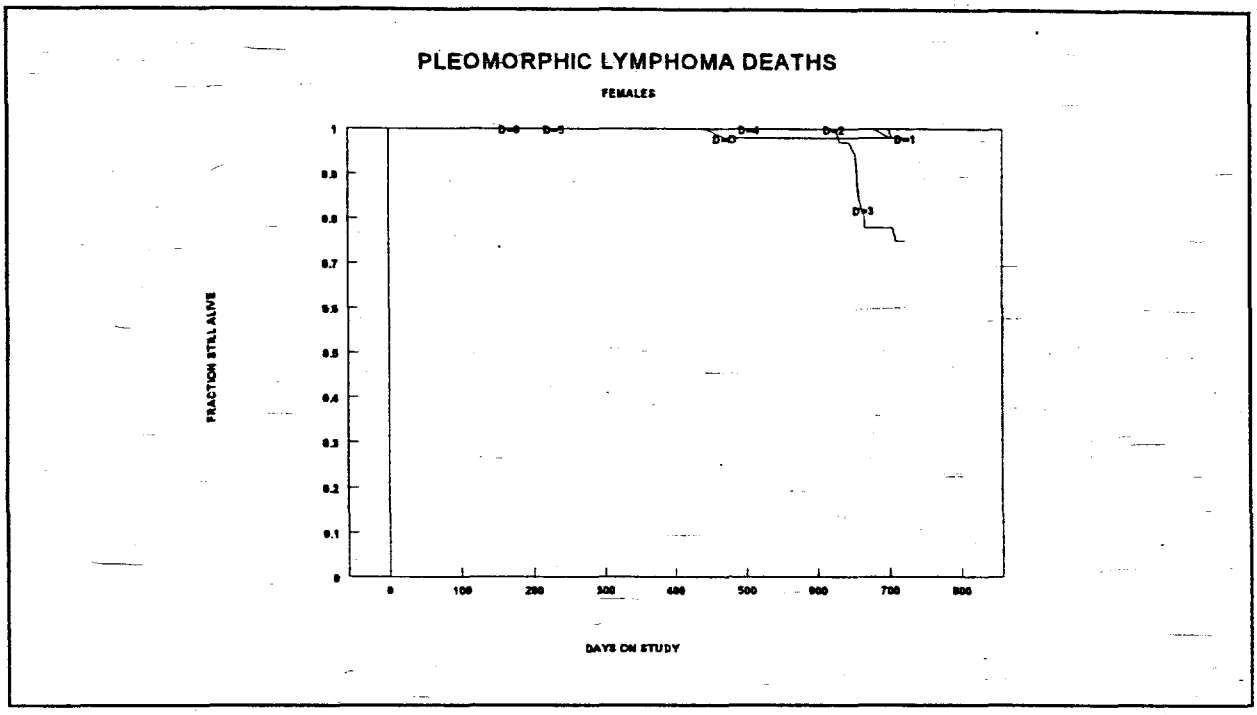

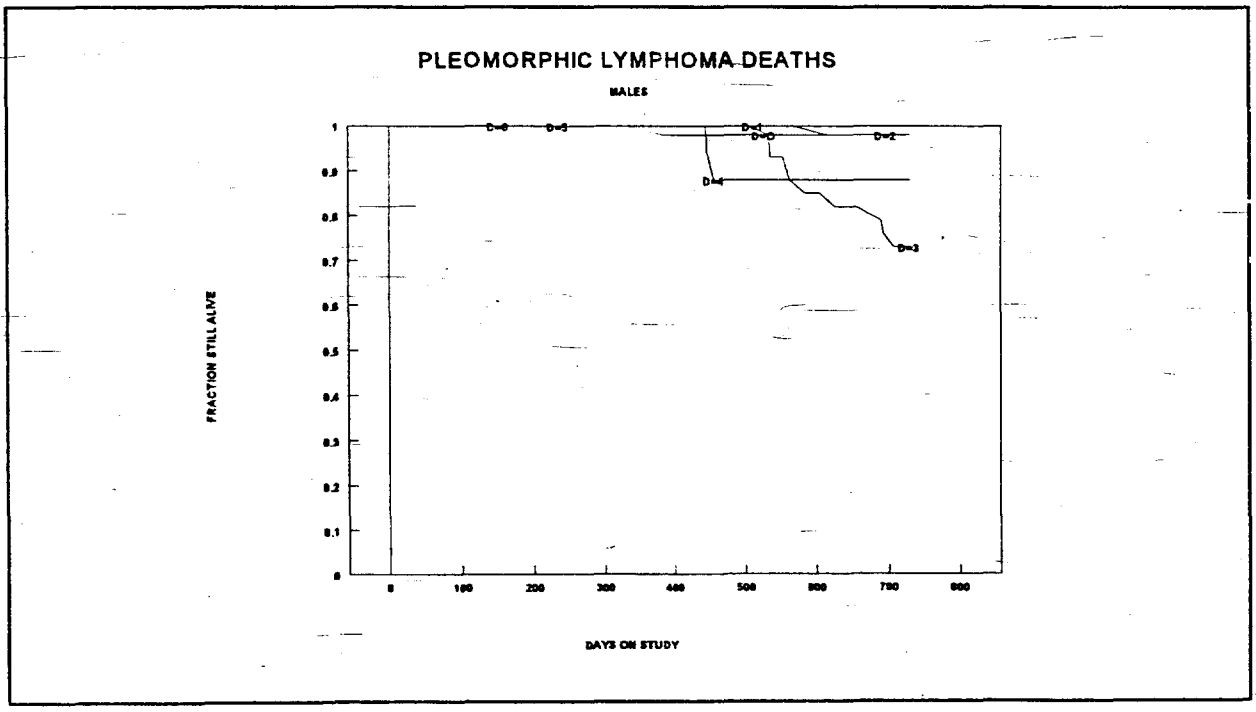

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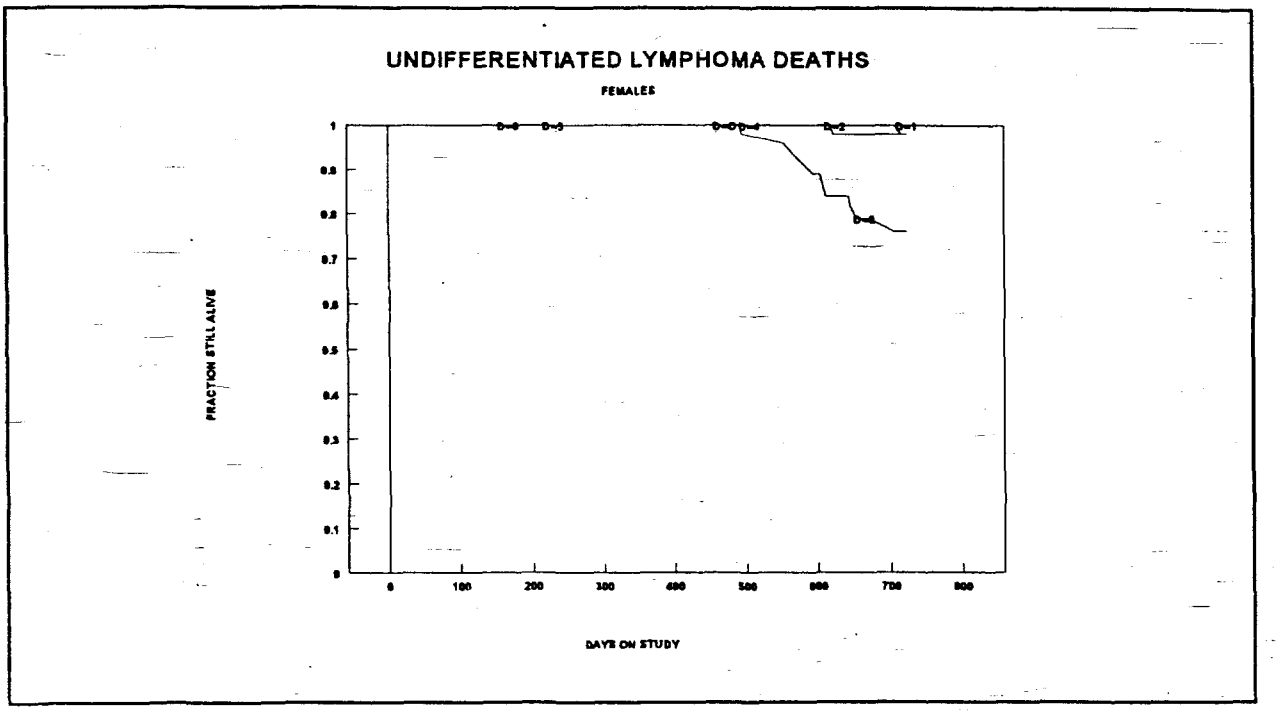

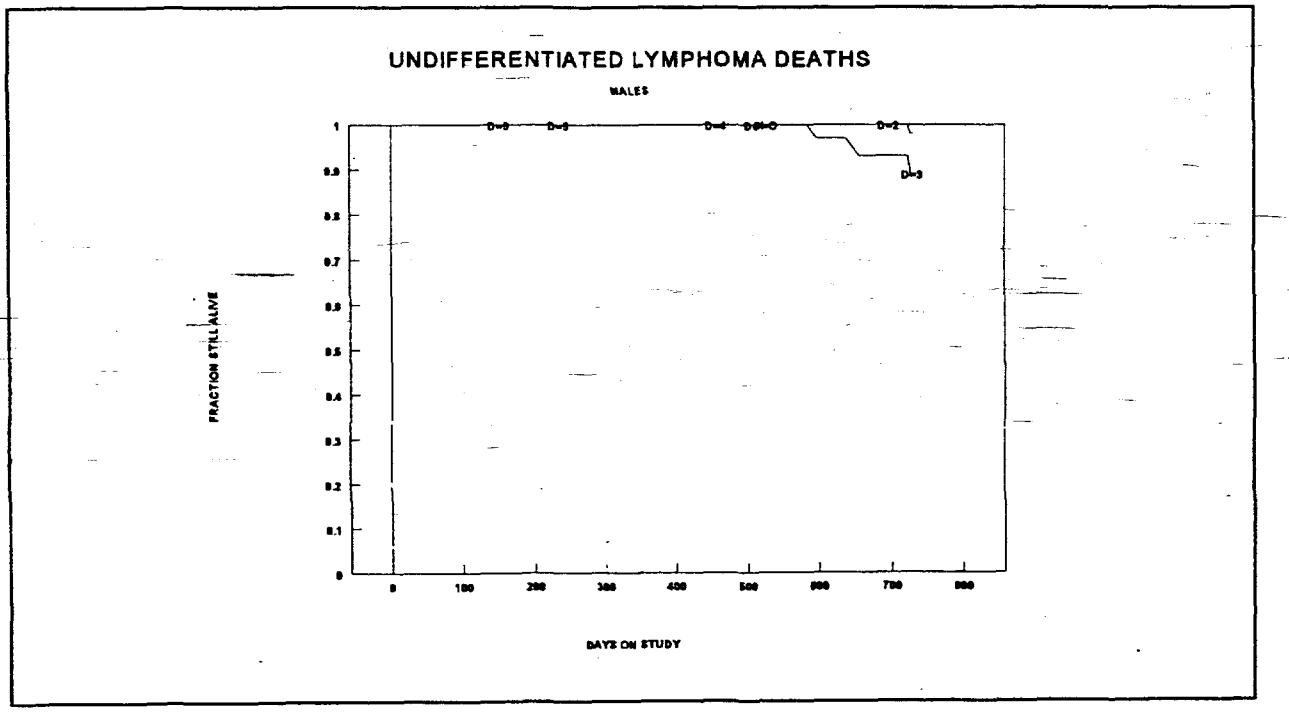

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IV. Conclusions:

The Kaplan-Meier curves for total mortality clearly show that doses up to and beyond the MTD were administered to the mice. There were also adequate numbers of mice alive for long enough at the approximate MTD (dose =0.1%) to assess carcinogenic potential.

Dermal application of Tacrolimus ointment was statistically significantly associated with the incidence of fatal hemolymphoretic tumors in both sexes of $B6C3F_1$ mice. Specifically, there was an increase in the incidence of pleomorphic and undifferentiated lymphomas. The time to death from these tumors was statistically significantly shorter in the highest dose group. The incidence rate was elevated mostly in the 0.1% dose group (the highest one with adequate long duration survival). The sponsor's assertion that there is no statistically significant increase in hemolymphoretic tumors in females is quite wrong.

There was also a statistically significant decrease in time to fatal hemolymphoretic tumor in both sexes, both p-values < 0.001.

There were no other statistically significant findings for any other organ system or tumor type other than those discussed above.

/S/

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

/S/ 2/29/2000

Concur: Dr. Al-Osh

cc:
Archival IND ——— (SN-124)
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Ms. Wright
HFD-540/Dr. Jacobs
HFD-540/Dr. Hill
HFD-725/Dr. Al-osh
HFD-725/Dr. Hammerstrom
HFD-725/Dr. Huque

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Statistical Review and Evaluation

NDA: 50-777
Name of Drug: Tacrolimus
Applicant: Fujisawa
Indication: Treatment of Atopic Dermatitis
Documents Reviewed: Vol. 59-Vol. 130 submitted on 9/8/99, and Vol. 1 submitted on 4/24/00
Medical Reviewer: Ramzy Labib, M.D.
Statistical Reviewer: Laura Lu, Ph.D.
Date of Review: 7/17/00

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I. Introduction

NDA 50-777 has been submitted for approval of tacrolimus ointment 0.03% and 0.1% for treatment of atopic dermatitis. A total of 15 Phase II or III studies were included in the NDA submission. This review will focus on efficacy of the three pivotal phase III trials: adult studies 035 and 036, and pediatric study 037.

II. Study Protocols

II.1 Study 97-0-035

This is a phase III, randomized, double-blind study comparing topically applied tacrolimus 0.03% and 0.1% ointment vs. vehicle ointment in adult patients with atopic dermatitis.

The duration of this study is 12 weeks plus a 2 weeks follow-up period. Patients were evaluated at prestudy (optional), baseline/Day 1, at Weeks 1, 2, 3, 6, 9, 12 and 14. The primary efficacy endpoint was the incidence of success obtained from the Physician's Global Evaluation ("Physician's Global") at the end of treatment. The Physician's Global, changes in the overall status of the atopic dermatitis lesions identified for treatment at baseline, was rated using the following scale:

	Percent Improvement
Cleared	100
Excellent Improvement	90 – 99
Marked Improvement	75 – 89
Moderate Improvement	50 – 74
Slight Improvement	30 – 49
No Appreciable Improvement	0 – 29
Worse	<0

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Success was defined as a rating of cleared or excellent improvement (90-100% improvement in areas defined for treatment at baseline). Secondary efficacy endpoints included: 1) Eczema Area and Severity Index (EASI; also known as [redacted] EASI), a composite score calculated based on the "Physician's Assessment of Individual Signs of Atopic Dermatitis" and determination of percent of body surface area affected; 2) the patient's perception of global improvement in disease status ("Patient's Assessment of

Overall Response") at the end of treatment; and 3) recurrence (defined as the reappearance or worsening of atopic dermatitis in the baseline defined treatment areas which warranted therapy) for patients considered treatment successes. Quality of Life (QOL) was conducted as an additional analysis.

A total of 300 patients were planned to be included in this study. Assuming the success rates were 20% for the vehicle group and 50% for the tacrolimus groups, the planned sample size can detect the 30% difference between the vehicle and tacrolimus groups with power at least 90% and α level 0.01. Since this α level is less than 0.05, the conventional level for statistical significance, the sample size in this study is larger than that when α=0.05 is used. The primary patient population for efficacy analyses was the evaluable patient subset comprised of all randomized patients who received study drug for at least 3 consecutive days (minimum of five applications) beginning at baseline/Day 1 and had at least one "on treatment" value for the Physician's Global. The modified intent-to-treat population (MITT) was defined as all patients who received at least one application of ointment. Usually, for efficacy evaluation we use the ITT population which includes every patient randomized and dispensed drug application. The difference of the results in evaluable, MITT and ITT populations will be discussed in the Reviewer's Comments section later.

The multiple comparisons between different treatment groups in Physician's Global were done by Fisher's LSD method with Fisher's exact test, i.e., Fisher's exact test was performed on the primary endpoint to determine if there was a statistically significant difference in the success rate among the three treatment groups; If statistical significance at the 5% level was obtained, Fisher's exact test was used for the pairwise comparison of three treatment groups, each at the 5% level of significance. Fisher's LSD method controls the overall type I error rate when the number of treatment is less than four. Treatment effect adjusted by center was analyzed by Cochran-Mantel- Haenszel (CMH) test stratified by center. Consistency of treatment effects among centers was assessed with the Breslow-Day test obtained during each pairwise comparison. The Patient's Assessment of Overall Response was analyzed by CMH test, and the EASI score was analyzed by ANOVA with baseline score as covariat. The analysis method for QOL was not prespecified in the protocol.

II.2 Study 97-0-036

The protocol of this study is identical to that of Study 97-0-035.

II.3 Study 97-0-037

The protocol of this study is identical to that of Study 97-0-035 except that the study population is pediatric patient (age 2-15).

III. Study Report

The results presented in this section are summarized from the sponsor's report for MITT population. The consistency of the sponsor's results in evaluable, MITT, and ITT population and this reviewer's results will be discussed in the Reviewer's Comment section later.

III.1 Study 97-0-035

III.1.1 Patient Disposition

A total of 304 patients received at least one dose of study drug and were included in the modified intent-to-treat population. The dropout rates were 62.7% in vehicle group, 29.1% in tacrolimus 0.03% group and 28.3% in tacrolimus 0.1% group. In the vehicle group, the main reason for dropouts were lack of efficacy (40.2%). In the tacrolimus groups, the main reasons for dropouts were administrative reason and lack of efficacy (13.6% and 10.7% in the 0.03% group, respectively; 11.1% and 10.1% in the 0.1% group, respectively.). The detailed information for patient disposition is summarized in Table a.1 of Appendix A.

III.1.2 Demographics

The treatment groups and patient populations were balanced with respect to age, race, and gender. The mean age was 39 years (range 15-77 years). The majority of patients were white and a quarter of the patients was black. On average, over 40% of the patients' total body surface area was affected at baseline, with 83% of patients being affected in the head/neck region. The majority of patients had severe atopic dermatitis. The detailed information for patient demographics is summarized in Table a.2 in Appendix A.

III.1.3 Efficacy Results

a. Primary Endpoint

A statistically significant difference ($p<0.001$) in success rate was observed among the three treatment groups. Therefore, each pairwise comparison of treatment groups was conducted. A significantly greater success rate was observed for each tacrolimus treatment group compared with the vehicle group. The observed success rate was about 6% higher in the 0.1% tacrolimus group compared with the 0.03% tacrolimus group, but this difference was not statistically significant ($p=0.369$). Success rates at the end of treatment and the distribution of the Physician's Global for the MITT population is presented in Table 1 below.

Table 1. Distribution of Physician's Global and Success Rate in Treatment Groups

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
	N=102	N=103	N=99
Cleared	0	7 (6.8%)	8 (8.1%)
Excellent Improvement	8 (7.8%)	23 (22.3%)	27 (27.3%)
Marked Improvement	12 (11.8%)	22 (21.4%)	19 (19.2%)
Moderate Improvement	8 (7.8%)	15 (14.6%)	18 (18.2%)
Slight Improvement	10 (9.8%)	16 (15.5%)	6 (6.1%)
No Appreciable Improvement	20 (19.6%)	9 (8.7%)	6 (6.1%)
Worse	36 (35.3%)	7 (6.8%)	9 (9.1%)
No Assessment	8 (7.8%)	4 (3.9%)	6 (6.1%)
Success	**8 (7.8%)**	**30 (29.1%)**	**35 (35.4%)**
P-value (vs. vehicle)		**<0.001**	**<0.001**

Source: Tables 8, 9 and 10 on pages 2-3 of attachment 5 of Vol.1 submitted on 4/24/00 for NDA 50777.

b. Secondary Endpoints

Small p-values ($p<0.001$) were observed between tacrolimus groups and vehicle for all secondary endpoints including EASI score, percent BSA affected, individual signs, patient's assessment of pruritus and patient's assessment of overall response. No statistical significance were found between the two tacrolimus groups in these endpoints and the numerical improvements were also similar. The distributions of Patient's Assessment of Overall Response in each treatment group are given in Table 2. Table 3 presents the least-square means (means adjusted by baseline and center effect) of change from baseline for EASI score, percent of BAS affected, pruritus score, total and individual sign scores.

Table 2. Patient's Assessment of Overall Response at the End of Treatment

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Total Number of Patients	N=102	N=103	N=99
Much Better	12 (11.8%)	37 (35.9%)	37 (37.4%)
Better	11 (10.8%)	29 (28.2%)	26 (26.3%)
Slightly Better	10 (9.8%)	11 (10.7%)	7 (7.1%)
Same	12 (11.8%)	5 (4.9%)	10 (10.1%)
Slightly Worse	11 (10.8%)	7 (6.8%)	2 (2.0%)
Worse	20 (19.6%)	5 (4.9%)	8 (8.1%)
Much Worse	16 (15.7%)	5 (4.9%)	2 (2.0%)
No Assessment	10 (9.8%)	4 (3.9%)	7 (7.1%)
P-value (vs. vehicle)		**<0.001**	**<0.001**

Source: Table 13 on page 6 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777

Table 3. Change from Baseline to the End of Treatment in EASI Score, Percent of BAS Affected, Pruritus Score, Total and Individual Sign Scores

Lease Squares Mean of Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
EASI			
N*	101	103	97
Least Squares Mean ± SE	-3.4 ± 1.02	-12.6 ± 1.01	-13.8 ± 1.04
P-value (vs. vehicle)		<0.001	<0.001
% BSA Affected			
N*	101	103	97
Least Squares Mean ± SE	-6.9 ± 1.81	-19.9 ± 1.79	-22.0 ± 1.85
P-value (vs. vehicle)		<0.001	<0.001
Patient's Assessment of Pruritus			
N*	101	102	97
Least Squares Mean ± SE	-0.7 ± 0.31	-3.8 ± 0.30	-3.6 ± 0.31
P-value (vs. vehicle)		<0.001	<0.001
Total Score			
N*	101	102	97
Least Squares Mean ± SE	-1.6 ± 0.41	-5.7 ± 0.41	-6.0 ± 0.42
P-value (vs. vehicle)		<0.001	<0.001
Edema			
N*	101	103	97
Least Squares Mean ± SE	-0.1 ± 0.07	-0.8 ± 0.07	-0.9 ± 0.07
P-value (vs. vehicle)		<0.001	<0.001
Erythema			
N*	101	103	97
Least Squares Mean ± SE	-0.2 ± 0.07	-0.9 ± 0.07	-0.8 ± 0.07
P-value (vs. vehicle)		<0.001	<0.001
Excoriation			
N*	101	103	97
Least Squares Mean ± SE	-0.2 ± 0.07	-0.7 ± 0.07	-0.8 ± 0.07
P-value (vs. vehicle)		<0.001	<0.001
Lichenification			
N*	101	103	97
Least Squares Mean ± SE	-0.2 ± 0.06	-0.8 ± 0.06	-0.8 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Oozing			
N*	101	103	97
Least Squares Mean ± SE	-0.1 ± 0.05	-0.4 ± 0.05	-0.4 ± 0.05
P-value (vs. vehicle)		<0.001	<0.001
Scaling			
N*	101	103	97
Least Squares Mean ± SE	-0.4 ± 0.06	-0.8 ± 0.06	-1.0 ± 0.07
P-value (vs. vehicle)		<0.001	<0.001

*: The total patient number was less than the number of the MITT population due to missing value in baseline scores.
Source: Tables 11-12 on pages 4-5 and tables on pages 7-8 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

III.2. Study 97-00-36

III.2.1 Patient Disposition

A total of 328 enrolled patients received at least one dose of study drug and was included in the modified intent-to-treat population. The dropout rates were 73.6% in vehicle group, 28.7% in tacrolimus 0.03% group and 21.8% in tacrolimus 0.1% group. The main reason for dropouts was lack of efficacy for the vehicle group and tacrolimus 0.03% group (49.1% and 13.9%, respectively) and administrative reason for the tacrolimus 0.1% group (10.9%). The detailed information for patient disposition is summarized in Table a.3 in Appendix A.

III.2.2 Demographics

The treatment groups and patient populations were balanced with respect to age, race, and gender. The mean age was 39 years (range 16-79 years). The majority of patients were white and a little more than a quarter of the patients were black. On average, about half of the patients' total body surface area was affected at baseline, with 91% of patients being affected in the head/neck region. The majority of patients had severe atopic dermatitis. The detailed information for patient demographics is summarized in Table a.4 in Appendix A.

III.2.3 Efficacy Results

a. Primary Endpoints

A statistically significant difference ($p<0.001$) in success rate was observed among the three treatment groups. Therefore, each pairwise comparison of treatment groups was conducted. A significantly greater success rate was observed for each tacrolimus treatment group compared with the vehicle group. In addition, a marginal significantly greater success rate was observed for the 0.1% tacrolimus treatment group compared with the 0.03% tacrolimus treatment group ($p=0.06$). Success rates at the end of treatment and the distribution of the Physician's Global for the MITT population is presented in Table 4 below.

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Table 4. Distribution of Physician's Global and Success Rate in Treatment Groups

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
	N=110	N=108	N=110
Cleared	2 (1.8%)	14 (13.0%)	12 (10.9%)
Excellent Improvement	4 (3.6%)	14 (13.0%)	30 (27.3%)
Marked Improvement	4 (3.6%)	17 (15.7%)	21 (19.1%)
Moderate Improvement	4 (3.6%)	18 (16.7%)	17 (15.5%)
Slight Improvement	16 (14.5%)	13 (12.0%)	13 (11.8%)
No Appreciable Improvement	30 (27.3%)	21 (19.4%)	9 (8.2%)
Worse	33 (30.0%)	6 (5.6%)	3 (2.7%)
No Assessment	17 (15.5%)	5 (4.6%)	5 (4.5%)
Success	**6 (5.5%)**	**28 (25.9%)**	**42 (38.2%)**
P-values (vs. vehicle)		**<0.001**	**<0.001**

Source: Tables 8, 9 and 10 on pages 10-11 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

b. Secondary Endpoints

Small p-values ($p<0.001$) were observed between tacrolimus groups and vehicle for all secondary endpoints including EASI score, percent BSA affected, individual signs, patient's assessment of pruritus and patient's assessment of overall response. No statistical significance was found between the two tacrolimus groups in these endpoints and the numerical improvements were also similar. The distributions of Patient's Assessment of Overall Response in each treatment group are given in Table 5. Table 6 presents the least-square means (means adjusted by baseline and center effect) of change from baseline for EASI score, percent of BAS affected, pruritus score, total and individual sign scores.

Table 5. Patient's Assessment of Overall Response at the End of Treatment

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Total Number of Patients	N=110	N=108	N=110
Much Better	4 (3.6%)	41 (38.0%)	45 (40.9%)
Better	10 (9.1%)	19 (17.6%)	26 (23.6%)
Slightly Better	13 (11.8%)	11 (10.2%)	12 (10.9%)
Same	18 (16.4%)	14 (13.0%)	11 (10.0%)
Slightly Worse	10 (9.1%)	9 (8.3%)	4 (3.6%)
Worse	20 (18.2%)	5 (4.6%)	3 (2.7%)
Much Worse	18 (16.4%)	4 (3.7%)	4 (3.6%)
No Assessment	17 (15.5%)	5 (4.6%)	5 (4.5%)
P-value (vs. vehicle)		<0.001	<0.001

Source: Tables 13 on page 14 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

Table 6. Change from Baseline to the End of Treatment in EASI Score, Percent of BAS Affected, Pruritus Score, Total and Individual Sign Scores

Least Squares Mean of Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
EASI			
N*	110	108	110
Least Squares Mean ± SE	-1.6 ± 0.97	-10.7 ± 0.98	-15.9 ± 0.97
P-value (vs. vehicle)		<0.001	<0.001
% BSA Affected			
N*	110	108	110
Least Squares Mean ± SE	-3.2 ± 1.68	-17.9 ± 1.69	-27.0 ± 1.68
P-value (vs. vehicle)		<0.001	<0.001
Patient's Assessment of Pruritus			
N*	107	107	109
Least Squares Mean ± SE	-0.6 ± 0.29	-3.1 ± 0.29	-3.5 ± 0.29
P-value (vs. vehicle)		<0.001	<0.001
Total Score			
N*	107	107	109
Least Squares Mean ± SE	-0.9 ± 0.36	-4.8 ± 0.36	-5.8 ± 0.36
P-value (vs. vehicle)		<0.001	<0.001
Edema			
N*	110	108	110
Least Squares Mean ± SE	-0.1 ± 0.06	-0.6 ± 0.06	-0.9 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Erythema			
N*	110	108	110
Least Squares Mean ± SE	-0.1 ± 0.06	-0.7 ± 0.06	-0.9 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Excoriation			
N*	110	108	110
Least Squares Mean ± SE	0.0 ± 0.06	-0.6 ± 0.06	-0.8 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Lichenification			
N*	110	108	110
Least Squares Mean ± SE	-0.1 ± 0.05	-0.6 ± 0.05	-0.7 ± 0.05
P-value (vs. vehicle)		<0.001	<0.001
Oozing			
N*	110	108	110
Least Squares Mean ± SE	0.0 ± 0.04	-0.2 ± 0.04	-0.3 ± 0.04
P-value (vs. vehicle)		<0.001	<0.001
Scaling			
N*	110	108	110
Least Squares Mean ± SE	-0.3 ± 0.06	-0.8 ± 0.07	-0.9 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001

*: The total patient number was less than the number of the MITT population due to missing value in baseline scores..
Source: Tables 11-12 on pages 12-13 and tables on pages 15-16 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

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III.3. Study 97-00-37

III.3.1. Patient Disposition

A total of 351 enrolled patients received at least one dose of study drug and was included in the modified intent-to-treat population (MITT). The dropout rates were 56.0% in vehicle group, 19.7% in tacrolimus 0.03% group and 14.4% in tacrolimus 0.1% group. In the vehicle group, the main reason for dropouts was lack of efficacy (39.7%). In the tacrolimus groups, the main reasons for dropouts was administrative reason (11.1% in the 0.03% and 7.6% in the 0.1% group). The detailed information for patient disposition is summarized in Table a.5 in Appendix A.

III.3.2. Demographics

The three treatment groups were comparable with respect to demographic distribution and baseline disease characteristics. Approximately half of the patients were male, and the mean age was 6 years. The majority of patients were white and a quarter of the patients were black. On average, nearly half of the patients' total body surface area was affected, with 84% of patients being affected in the head/neck region. The majority of patients had severe atopic dermatitis. The detailed information for patient demographics is summarized in Table a.6 in Appendix A.

III.3.3. Efficacy Results

a. Primary Endpoint

A statistically significant difference ($p<0.001$) in success rate was observed among the three treatment groups. Therefore, each pairwise comparison of treatment groups was conducted. A significantly greater success rate was observed for each tacrolimus treatment group compared with the vehicle group ($p<0.001$). The success rate in the tacrolimus 0.1% groups (40.7%) was higher than that in the tacrolimus 0.03% group (35.9%), but the difference was not statistically significant ($p=0.401$). Success rates at the end of treatment and the distribution of the Physician's Global for the MITT population is presented in Table 7 below.

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Table 7. Distribution of Physician's Global and Success Rate in Treatment Groups

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
	N=116	N=117	N=118
Cleared	4(3.4%)	14(12.0%)	13(11.0%)
Excellent Improvement	4(3.4%)	28(23.9%)	35(29.7%)
Marked Improvement	10(8.6%)	23(19.7%)	19(16.1%)
Moderate Improvement	13(11.2%)	20(17.1%)	25(21.2%)
Slight Improvement	19(16.4%)	15(12.8%)	12(10.2%)
No Appreciable Improvement	27(23.3%)	10(8.5%)	7(5.9%)
Worse	28(24.1%)	2(1.7%)	2(1.7%)
No Assessment	17(15.5%)	5 (4.6%)	5 (4.5%)
Success	**8(6.9%)**	**42(35.9%)**	**48(40.7%)**
P-value (vs. vehicle)		**<0.001**	**<0.001**

Source: Tables 9, 10 and 11 on pages 18-19 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

b. Secondary Endpoints

Small p-values ($p<0.001$) were observed between tacrolimus groups and vehicle for all secondary endpoints including EASI score, percent BSA affected, individual signs, patient's assessment of pruritus and patient's assessment of overall response. No statistical significance were found between the two tacrolimus groups in these endpoints and the numerical improvements were also similar. The distributions of Patient's Assessment of Overall Response in each treatment group are given in Table 8. Table 9 presents the least-square means (means adjusted by baseline and center effect) of change from baseline for EASI score, percent of BAS affected, pruritus score, total and individual sign scores.

Table 8. Patient's Assessment of Overall Response at the End of Treatment

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Total Number of Patients	N=116	N=117	N=118
Much Better	8 (6.9%)	56 (47.9%)	70 (59.3%)
Better	17 (14.7%)	27 (23.1%)	21 (17.8%)
Slightly Better	20 (17.2%)	10 (8.5%)	11 (9.3%)
Same	21 (18.1%)	11 (9.4%)	3 (2.5%)
Slightly Worse	13 (11.2%)	4 (3.4%)	5 (4.2%)
Worse	15 (12.9%)	3 (2.6%)	2 (1.7%)
Much Worse	10 (8.6%)	0 (0.0%)	1 (0.8%)
No Assessment	12 (10.3%)	6 (5.1%)	5 (4.2%)
P-value (vs. vehicle)		<0.001	<0.001

Source: Table 14 on pages 22 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777

Table 9. Change from Baseline to the End of Treatment in EASI Score, Percent of BAS Affected, Pruritus Score, Total and Individual Sign Scores

Least Squares Mean of Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
EASI			
N*	116	117	118
Least Squares Mean ± SE	-2.4 ± 0.99	-14.0 ± 0.95	-15.0 ± 0.95
P-value (vs. vehicle)		<0.001	<0.001
% BSA Affected			
N*	116	117	118
Least Squares Mean ± SE	-6.4 ± 1.98	-26.4 ± 1.90	-27.5 ± 1.91
P-value (vs. vehicle)		<0.001	<0.001
Patient's Assessment of Pruritus			
N*	116	116	116
Least Squares Mean ± SE	-0.8 ± 0.30	-3.9 ± 0.29	-3.9 ± 0.29
P-value (vs. vehicle)		<0.001	<0 001
Total Score			
N*	116	116	116
Least Squares Mean ± SE	-1.5 ± 0.36	-5.8 ± 0.34	-6.1 ± 0.35
P-value (vs. vehicle)		<0.001	<0.001
Edema			
N*	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.7 ± 0.06	-0.8 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Erythema			
N*	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.8 ± 0.06	-0.8 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Excoriation			
N*	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.7 ± 0.06	-0.9 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Lichenification			
N*	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.8 ± 0.05	-0.7 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001
Oozing			
N*	116	117	118
Least Squares Mean ± SE	0.0 ± 0.05	-0.5 ± 0.05	-0.5 ± 0.05
P-value (vs. vehicle)		<0.001	<0.001
Scaling			
N*	116	117	118
Least Squares Mean ± SE	-0.3 ± 0.06	-0.9 ± 0.06	-1.0 ± 0.06
P-value (vs. vehicle)		<0.001	<0.001

*: The total patient number was less than the number of the MITT population due to missing value in baseline scores.
Source: Tables 11-12 on pages 20-21 and tables on pages 23-24 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

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IV. Safety Report

Numbers of adverse events were combined across three pivotal studies (035, 036, and 037). The incidence rates of adverse events were compared by normal approximation test based on Kaplan-Meier estimates which takes account the discontinuation of patients. The incidence number and rates for adverse events that with p-value less than 0.05 for between treatment comparisons are listed in Table 10 below. The p-values serve as alarms and can not be interpreted on their face values due to the fact that the studies were not designed for testing such hypotheses and also due to the multiple comparisons.

Table 10. Adjusted Incidence Rates For Adverse Events With P-value<0.05 In Three Pivotal Studies (035, 036, 037)

Adverse Events (COSTART system)	Treatment Groups Vehicle (N=328) n (%)	0.03% (N=328) n (%)	0.1% (N=327) n (%)	P-value+ 0.03% vs. Vehicle	0.1% vs. Vehicle
ALCOHOL INTOLERANCE	0(0.0%)	6(1.8%)	12(3.7%)	0.014*	<0.001*
CYST	0(0.0%)	2(0.6%)	4(1.2%)	0.159	0.047*
ALLERGIC REACTION	13(4.0%)	25(7.6%)	12(3.7%)	0.675	0.203
FLU SYNDROME	41(12.5%)	69(21.0%)	85(26.0%)	0.476	0.033*
DYSPEPSIA	2(0.6%)	2(0.6%)	8(2.4%)	0.934	0.048*
MYALGIA	0(0.0%)	5(1.5%)	4(1.2%)	0.026*	0.046*
HEADACHE	20(6.1%)	42(12.8%)	48(14.7%)	0.152	0.040*
HYPERESTHESIA	1(0.3%)	6(1.8%)	13(4.0%)	0.054	0.001*
ACNE	3(0.9%)	8(2.4%)	13(4.0%)	0.300	0.030*
FOLLICULITIS	1(0.3%)	14(4.3%)	9(2.8%)	0.001*	0.010*
HERPES ZOSTER	0 (0.0%)	5(1.5%)	1(0.3%)	0.026*	0.316
PRURITUS	96(29.3%)	141(43.0%)	128(39.1%)	0.007*	0.054
SKIN BURNING	77(23.5%)	143(43.6%)	156(47.7%)	<0.001*	<0.001*
SKIN INFECTION	27(8.2%)	32(9.8%)	18(5.5%)	0.971	0.095
SKIN TINGLING	6(1.8%)	9(2.7%)	15(4.6%)	0.482	0.048*

+ P-values are from normal approximation test based on Kaplan-Meier estimates.
* p-value less than 0.05
Source: APPENDIX 8.4.13.6.1.1 on pages 164-169 and APPENDIX 8.4.13.6.2.2 on pages 171-175 of Vol.122 of NDA 50777 submitted on 9/8/99.

The sponsor also submitted the estimated average hazard rate for adverse events in patients with tacrolimus 0.1% during the first 3 months, 6 months and 12 months by combining Studies Fg06-12, 96-0-025, 97-0-035, 97-0-036 and 97-0-037. The adverse events with an increasing estimated hazard rate over the time periods are listed in Table 11 below.

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Table 11. Daily Hazard Rates* Over Time For Adverse Events - Long-Term Studies And Short-Term Studies (MITT Population in Tacrolimus 0.1%)**

COSTART TERM	DAY 1- 90 HAZARD(SE)	DAY 91-182 HAZARD(SE)	DAY 183-366 HAZARD(SE)
PROCEDURAL COMPLICATION	0.000 ( )	0.023 (0.0232)	0.044 (0.0312)
AORTIC STENOSIS	0.000 ( )	0.000 ( )	0.022 (0.0220)
GASTROINTESTINAL HEMORRHAGE	0.000 ( )	0.000 ( )	0.022 (0.0220)
RECTAL DISORDER	0.000 ( )	0.000 ( )	0.022 (0.0220)
LYMPHADENOPATHY	0.075 (0.0338)	0.093 (0.0466)	0.111 (0.0497)
HYPERCHOLESTEREMIA	0.000 ( )	0.000 ( )	0.022 (0.0220)
HYPOGLYCEMIA	0.000 ( )	0.000 ( )	0.044 (0.0311)
HYPOMAGNESEMIA	0.000 ( )	0.000 ( )	0.022 (0.0220)
DEPRESSION	0.015 (0.0151)	0.046 (0.0328)	0.044 (0.0312)
HYPERTONIA	0.000 ( )	0.023 (0.0231)	0.022 (0.0220)
HYPOTONIA	0.000 ( )	0.000 ( )	0.022 (0.0220)
SLEEP DISORDER	0.000 ( )	0.000 ( )	0.022 (0.0220)
THINKING ABNORMAL	0.000 ( )	0.000 ( )	0.022 (0.0220)
SEBORRHEA	0.000 ( )	0.023 (0.0232)	0.066 (0.0381)
KERATITIS	0.000 ( )	0.023 (0.0232)	0.044 (0.0312)

* Hazard Rate (x1000) For 1-90 Day, 91-182 Day And 183-366 Day Based On The Life Table Method.
** Long-Term Studies: Fg06-12 And 96-0-025, Short-Term Studies: 97-0-035, 97-0-036 And 97-0-037.
Source: Attachment 3 of Vol.1 of NDA 50777 submitted on 4/21/00.

V. Reviewer's Comments

1. Consistency of Results

The Sponsor submitted efficacy results for both MITT and evaluable population. The sponsor's results for the MITT population are in agreement with that of this reviewer and are also consistent with that of the evaluable population. The ITT population, which includes all patients that are randomized and dispensed medication is the same as the MITT population in all three studies.

2. Treatment by Center Interaction

In Study 035, the p-value for treatment by center interaction between the 0.03% tacrolimus group and the vehicle group was less then 0.05 (p=0.03). This small p-value might be due to heterogeneity of patients and clinical settings in each center, or pure chance. Three (3) out of the 21 centers had reversed treatment effect, i.e., the vehicle group had higher success rate than the 0.03% tacrolimus group. The success rate in the three centers are listed in the table below which shows that the success rate in the 0.03% group in each center is in the range of the overall success rate (29.1%), while those in the vehicle groups are much higher than the overall success rate (7.8%).

Table 12. Success Rate in Centers with Reversed Treatment Effect

Center Number	Vehicle	0.03% Tacrolimus
84 (Michigan)	2/6 (33.3%)	1/5 (20.0%)
236 (Hill Top, Birmingham)	3/6 (50.0%)	1/5 (20.0%)
237 (Hill Top, Colombus)	2/4 (50.0%)	1/4 (25.0%)

Source: APPENDIX 14.2.2.1.1 on page 326 of section 8.1.1.2 of NDA 50777 (Vol.64)

To further explore the cause of treatment by center interaction, this reviewer analyzed and listed the demographics of the patients in the treatment groups of each center in the table below. There is no consistent difference between the demographics in the three centers and the overall patients in Study 035. Although the baseline percent of body surface area effected in the three centers are imbalanced, the directions of imbalance in the three centers are not the same. However, it should be noted that the number of patients is relatively small and consequently we will not pursue this further.

Table 13. Demographics in Centers with Reversed Treatment Effect

Variable	Center						Total in Study 035
	84		236		237		
Treatment	Vehicle	0.03%	Vehicle	0.03%	Vehicle	0.03%	
# of Patients	6	5	6	5	4	4	304
Gender							
Female	3 (50.0%)	4 (80.0%)	2 (33.3%)	3 (60.0%)	1 (25.0%)	1 (25.0%)	175 (57.6%)
Male	3 (50.0%)	1 (20.0%)	4 (66.7%)	2 (40.0%)	3 (75.0%)	3 (75.0%)	129 (42.4%)
Race							
White	5 (63.3%)	4 (80.0%)	2 (33.3%)	5 (100.0%)	1 (25.0%)	3 (75.0%)	202 (66.4%)
Black	1 (26.7%)	1 (20.0%)	4 (66.7%)	0 (0.0%)	3 (75.0%)	1 (25.0%)	84 (27.6%)
Age (yrs)							
Mean (SD)	50.0 (19.0)	27.4 (15.2)	32.2 (11.0)	37.6 (9.6)	44.3 (12.8)	40.8 (8.1)	38.6 (13.5)
Severity							
Moderate	2 (33.3%)	1 (20.0%)	2 (33.3%)	1 (20.0%)	1 (25.0%)	2 (50.0%)	142 (46.7%)
Severe	4 (66.7%)	4 (80.0%)	4 (66.7%)	4 (80.0%)	3 (75.0%)	2 (50.0%)	162 (53.3%)
% BSA Affected							
Mean (SD)	51.0 (31.8)	22.5 (7.8)	28.3 (11.8)	57.0 (34.2)	65.3 (29.3)	21.8 (13.9)	42.4 (25.4)

3. Influence of Drop-Outs in Efficacy Results

The overall dropout rates are around 40% in the adult studies (035 and 036) and 30% in the children study (037). The Sponsor imputed the dropout data by last observation carried forward method. So a patient was classified as a treatment success as long as the last measurement before the drop-out time was classified as a treatment success, even if the patient dropped out of the study due to lack of efficacy or adverse event. Since 'lack of efficacy' or 'adverse events' are reasons that reflect the failure of a treatment, and 'administrative reason' may not be treatment related, to assess the sensitivity of the efficacy results, this reviewer reanalyzed the primary endpoint by imputing the dropout data with a modified worst case method:

a). All patients who dropped out due to lack of efficacy or adverse events are classified as treatment failures.

b). For patients dropped out due to administrative reason, if the patient was in the vehicle group, the patient is classified as a treatment success, otherwise the patient is classified as a treatment failure.

The results from this analysis are consistent with those of the sponsor's in terms of p-values as presented in the tables below.

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Table 14. Incidence of Success by Modified Worst Case Analysis

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Study 035 Success rate P-value (vs. vehicle)	19/120 (16%)	29/103 (28%) <0.001	33/99 (33%) <0.001
Study 036 Success rate P-value (vs. vehicle)	19/110 (17%)	28/108 (26%) <0.001	42/110 (38%) <0.001
Study 037 Success rate P-value (vs. vehicle)	17/116 (15%)	39/117 (33%) <0.001	48/118 (41%) <0.001

4. Quality of Life Measurement

Quality of Life (QOL) measurement was not specified as a primary or secondary efficacy endpoint in the protocol, and the analysis method for QOL was also not specified in the protocol. Based on medical officer's opinion, QOL does not have sufficient validation. So the result on QOL should not be claimed in the label.

VI. Final Conclusion

The results of the efficacy analyses have demonstrated efficacy of 0.03% and 0.1% tacrolimus against vehicle in both adult patients (Studies 035 and 036) and pediatric patients (Study 037). The success rates of Physician's Global (primary efficacy endpoint) were numerically higher in the 0.1% tacrolimus group than that in the 0.03% tacrolimus group in all three studies, but no statistical significance was found.

/S/

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Concur:

/S/

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CC:
Archival NDA 21-145
HFD-540/MO/Labib
HFD-540/Okun
HFD-540/Wilkin
HFD-540/Wright
HFD-725/Lu
HFD-725/Alosh
HFD-725/Huque
HFD-725/Div. File

This review consists of 16 pages including one appendix of 3 pages.

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Appendix A. Tables

Table a.1 Patient Disposition (Study 035)

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Modified Intent to Treat	102	103	99
Completed Treatment	38(37.3%)	73(70.9%)	71(71.7%)
Discontinued Treatment	64(62.7%)	30(29.1%)	28(28.3%)
Lack of Efficacy	41(40.2%)	11(10.7%)	10(10.1%)
Adverse Event	12(11.8%)	5(4.9%)	7(7.1%)
Administrative Reason	11(10.8%)	14(13.6%)	11(11.1%)
Discontinuation Day			
Mean ± SD	20.6 ± 17.9	35.9 ± 23.9	27.8 ± 22.9
Median	15.0	30.0	22.0

Source: Table 2 on page 53 of section 8.1.1.2 (Vol.64) of NDA 50777 submitted on 9/8/00.

Table a.2 Baseline Demographics and Patient Characteristics (Study 035)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Total # of Patients	102	103	99	304
Gender				
Female	52 (51.0%)	62 (60.2%)	61 (61.6%)	175 (57.6%)
Male	50 (49.0%)	41 (39.8%)	38 (38.4%)	129 (42.4%)
Race				
White	67 (65.7%)	69 (67.0%)	66 (66.7%)	202 (66.4%)
Black	30 (29.4%)	28 (27.2%)	26 (26.3%)	84 (27.6%)
Oriental	3 (2.9%)	5 (4.9%)	5 (5.1%)	13 (4.3%)
Other	2 (2.0%)	1 (1.0%)	2 (2.0%)	5 (1.6%)
Ethnicity				
Nonhispanic	99 (97.1%)	101 (98.1%)	93 (93.9%)	293 (96.4%)
Hispanic	3 (2.9%)	2 (1.9%)	6 (6.1%)	11 (3.6%)
Age (yrs)				
Mean ± SD	38.6 ± 13.8	38.0 ± 13.8	39.3 ± 13.0	38.6 ± 13.5
Median	36.0	37.0	38.0	37.0
Range	16 – 75	15 – 72	17 – 77	15 – 77
Severity				
Moderate	49 (48.0%)	54 (52.4%)	39 (39.4%)	142 (46.7%)
Severe	53 (52.0%)	49 (47.6%)	60 (60.6%)	162 (53.3%)
% BSA Affected				
Mean ± SD	43.4 ± 24.5	41.4 ± 25.1	42.4 ± 26.7	42.4 ± 25.4
Median	37.3	35.0	33.0	35.0
Range	11.2 – 98.0	10.0 – 100.0	10.0 – 100.0	10.0 – 100.0
Head/Neck Affected	91 (89.2%)	82 (79.6%)	79 (79.8%)	252 (82.9%)

Source: Table 3 on page 1 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

Table a.3 Patient Disposition (Study 036)

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Modified Intent to Treat	110	108	110
Completed Treatment	29(26.4%)	77(71.3%)	86(78.2%)
Discontinued Treatment	81(73.6%)	31(28.7%)	24(21.8%)
Lack of Efficacy	54(49.1%)	15(13.9%)	8(7.3%)
Adverse Event	14(12.7%)	8(7.4%)	4(3.6%)
Administrative Reason	13(11.8%)	8(7.4%)	12(10.9%)
Discontinuation Day			
Mean ± SD	18.0 ± 18.1	36.6 ± 25.1	20.5 ± 19.9
Median	13	36	15

Source: Table 2 on page 53 of section 8.1.1.3 (Vol.68) of NDA 50777 submitted on 9/8/00.

Table a.4 Baseline Demographics and Patient Characteristics (Study 036)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Total # of Patients	110	108	110	328
Gender				
Female	65 (59.1%)	54 (50.0%)	63 (57.3%)	182 (55.5%)
Male	45 (40.9%)	54 (50.0%)	47 (42.7%)	146 (44.5%)
Race				
White	73 (66.4%)	75 (69.4%)	73 (66.4%)	221 (67.4%)
Black	27 (24.5%)	27 (25.0%)	29 (26.4%)	83 (25.3%)
Oriental	7 (6.4%)	4 (3.7%)	7 (6.4%)	18 (5.5%)
Other	3 (2.7%)	2 (1.8%)	1 (0.9%)	6 (1.8%)
Ethnicity				
Nonhispanic	108 (98.2%)	107 (99.1%)	105 (95.5%)	320 (97.6%)
Hispanic	2 (1.8%)	1 (0.9%)	5 (4.5%)	8 (2.4%)
Age (yrs)				
Mean ± SD	38.5 ± 14.3	37.9 ± 13.8	39.2 ± 15.8	38.5 ± 14.6
Median	39	37	39	38
Range	16 – 73	16 – 76	16 – 79	16 – 79
Severity				
Moderate	49 (44.5%)	39 (36.1%)	47 (42.7%)	135 (41.2%)
Severe	61 (55.5%)	69 (63.9%)	63 (57.3%)	193 (58.8%)
% BSA Affected				
Mean ± SD	47.4 ± 26.7	48.2 ± 28.0	47.2 ± 27.2	47.6 ± 27.2
Median	43.8	42.3	43.3	42.8
Range	10.0 – 98.6	10.0 – 100.0	10.0 – 100.0	10.0 – 100.0
Head/Neck Affected	98 (89.1%)	100 (92.6%)	100 (90.9%)	298 (90.9%)

Source: Table 3 on page 9 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.

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Table a.5 Patient Disposition (Study 036)

Variable	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Modified Intent to Treat	116	117	118
Completed Treatment	51(44.0%)	94(80.3%)	101(85.6%)
Discontinued Treatment	65(56.0%)	23(19.7%)	17(14.4%)
Lack of Efficacy	46(39.7%)	4 (3.4%)	5 (4.2%)
Adverse Event	9 (7.8%)	6 (5.1%)	3 (2.5%)
Administrative Reason	10(8.6%)	13(11.1%)	9 (7.6%)
Discontinuation Day			
Mean ± SD	22.4 ± 20.0	30.4 ± 26.6	21.4 ± 16.1
Median	21	23	22

Source: Table 2 on page 50 of section 8.1.1.1 (Vol.59) of NDA 50777 submitted on 9/8/00.

Table a.6 Baseline Demographics and Patient Characteristics (Study 037)

Variable		Treatment Group			Total
		Vehicle	Concentration of Tacrolimus Ointment		
			0.03%	0.1%	
Total # of Patients		116	117	118	351
Gender					
Female		63 (54.3%)	62 (53.0%)	61 (51.7%)	186 (53.0%)
Male		53 (45.7%)	55 (47.0%)	57 (48.3%)	165 (47.0%)
Race					
White		78 (67.2%)	76 (65.0%)	75 (63.6%)	229 (65.2%)
Black		28 (24.1%)	32 (27.4%)	34 (28.8%)	94 (26.8%)
Oriental		8 (6.9%)	7 (6.0%)	6 (5.1%)	21 (6.0%)
Other		2 (1.7%)	2 (1.7%)	3 (2.5%)	7 (2.0%)
Ethnicity					
Nonhispanic		107 (92.2%)	112 (95.7%)	112 (94.9%)	331 (94.3%)
Hispanic		9 (7.8%)	5 (4.3%)	6 (5.1%)	20 (5.7%)
Age (yrs)					
Mean ± SD		5.8 ± 3.3	6.1 ± 3.8	6.4 ± 3.7	6.1 ± 3.6
Median		5	5	6	5
Range		2 – 15	2 – 15	2 – 15	2 – 15
Severity	Moderate	47 (40.5%)	45 (38.5%)	43 (36.4%)	135 (38.5%)
	2-6 years	27 (37.5%)	26 (35.1%)	22 (31.9%)	75 (34.9%)
	7-15 years	20 (45.5%)	19 (44.2%)	21 (42.9%)	60 (44.1%)
	Severe	69 (59.5%)	72 (61.5%)	75 (63.6%)	216 (61.5%)
	2-6 years	45 (62.5%)	48 (64.9%)	47 (68.1%)	140 (65.1%)
	7-15 years	24 (54.5%)	24 (55.8%)	28 (57.1%)	76 (55.9%)
% BSA	Mean ± SD	49.2 ± 28.8	45.6 ± 27.5	48.3 ± 24.8	47.7 ± 27.1
Affected	2-6 years	48.1 ± 28.8	46.2 ± 27.9	51.1 ± 23.9	48.4 ± 26.9
	7-15 years	51.0 ± 29.2	44.5 ± 27.2	44.4 ± 25.9	46.6 ± 27.4
Head/Neck		100 (86.2%)	100 (85.5%)	93 (78.8%)	293 (83.5%)
Affected	2-6 years	64 (88.9%)	62 (83.8%)	56 (81.2%)	182 (84.7%)
	7-15 years	36 (81.8%)	38 (88.4%)	37 (75.5%)	111 (81.6%)

Source: Table 3 on page 17 of attachment 5, Vol.1 submitted on 4/24/00 for NDA 50777.